PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf)** and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Determining Whether Ethnic Minorities with Severe Obesity Face a Disproportionate Risk of Serious Disease and Death from COVID-19: Outcomes from a Southern California Based Retrospective Cohort Study
AUTHORS	Patel, Hemesh; Khandwala, Shefali; Somani, Poonam; Li, Qiaowu; Tovar, Stephanie; Montano, Alejandra

VERSION 1 – REVIEW

REVIEWER	Kengo Nagashima Keio University Hospital, Biostatistics Unit, Clinical and Translational Research Center
REVIEW RETURNED	15-Dec-2021

GENERAL COMMENTS	In this manuscript, the authors investigated ethnic minorities, obesity (BMI) and their interaction with hospitalization, invasive ventilation and mortality for COVID-19. Statistical analyses were generally conducted appropriately, but I have a few comments. 1. Categorization of continuous variables Since categorization of continuous variables is known to be problematic, it is better to also perform the analysis using continuous variables. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ 2006; 332: 1080. DOI: https://doi.org/10.1136/bmj.332.7549.1080 2. Missing data Since the method for handling missing data is not described, please add a description of how to address missing data. If you were conducted complete-case analyses, it would be desirable to consider applying multiple imputation or other appropriate methods as sensitivity analyses. 3. STROBE Statement checklist Please add item 12 as it is blank.

REVIEWER	Indrikis Krams University of Tartu
REVIEW RETURNED	30-Dec-2021

GENERAL COMMENTS	bmjopen-2021-059132 This is a precious and well-written paper. It will be of interest to the

wide community of physicians and biomedical scientists. I have only one comment, and I believe the paper can be published almost as it stands.

My lab has recently proposed an idea of a more severe outcome of the COVID-19 disease in Western countries which is based on differences in the fattening strategies between Asians and Europeans. The amount of visceral adipose tissue (VAT) is among the most important predictors in our theoretical research. You wrote that "When we adjusted BMI for Asian patients, we did not find a striking difference in trends in our results…". Could you please elaborate more on your results in light of our hypothesis? As far as I understood, you did not measure VAT directly in your study? Please, consider the following papers of my lab:
Krams et al. 2021 Int J Environ Res Public Health 18: 1029. doi.org/10.3390/ijerph18031029
Krams et al. 2020 Pathogens 9: 887. doi.org/10.3390/pathogens9110887
Krams et al. 2018. J Exp Biol 221. doi: 10.1242/jeb.184499

I. A. Krams

REVIEWER	Nicholas Finer UCL, Bariatric Medicine and Surgery
REVIEW RETURNED	01-Mar-2022

| GENERAL COMMENTS | The authors have examined the KP Southern California health records to explore the impact of obesity and ethnicity on COVID-19 severity. These are important findings that have both clinical and research implications.

Major points:

There is no information on vaccination status which surely differs between age and ethnic groups?

The paper is not written in patient-first language e.g. obese Black patients should be Black patients with obesity. (e.g., https://odr.dc.gov/page/people-first-language); morbid obesity is an archaic term – severe obesity is preferred.

Most of the positive findings relate to those with a BMI >40 or >45. As such should the title be '…with SEVERE obesity…'?

With the now (2022) dominance of the (probably milder) omicron variant, it might be worth including a mention of the dominant strain of COVID-19 present at the time of the study.

There is much focus (in the discussion) of a potential 'obesity paradox'. Firstly, many prefer the term 'BMI paradox' to obesity paradox, since it is the wide variance of %body fat at any BMI that may contribute to the 'paradox'. Although the authors allude to, and cite some of the literature on the contrary findings relating BMI to severity and outcomes, they do not address the fundamental flaws (such as reverse causality, collider bias etc.) around this concept, that in this reviewer's opinion hugely undermine its validity, e.g. some of many publications

Peeters A. Journals should no longer accept 'obesity paradox' articles. Int J Obes (Lond). 2018;42:584-5. doi: 10.1038/ijo.2017.259 |

	Martin-Ponce E, Santolaria F, Aleman-Valls MR, Gonzalez-Reimers E, Martinez-Riera A, Rodriguez-Gaspar M, et al. Factors involved in the paradox of reverse epidemiology. Clin Nutr. 2010;29:501-6. doi: 10.1016/j.clnu.2009.12.009
	Vansteelandt S. Asking Too Much of Epidemiologic Studies: The Problem of Collider Bias and the Obesity Paradox. Epidemiology. 2017 Sep;28(5):e47-e49. doi: 10.1097/EDE.0000000000000693. PMID: 28574920.
	De Jong A, Wrigge H, Hedenstierna G, Gattinoni L, Chiumello D, Frat JP, Ball L, Schetz M, Pickkers P, Jaber S. How to ventilate obese patients in the ICU. Intensive Care Med. 2020 Dec;46(12):2423-2435. doi: 10.1007/s00134-020-06286-x. Epub 2020 Oct 23. PMID: 33095284; PMCID:
	Lee DH, Giovannucci EL. The Obesity Paradox in Cancer: Epidemiologic Insights and Perspectives. Curr Nutr Rep. 2019 Sep;8(3):175-181. doi: 10.1007/s13668-019-00280-6. PMID: 31129887.
	Preston SH, Stokes A. Obesity paradox: conditioning on disease enhances biases in estimating the mortality risks of obesity. Epidemiology. 2014 May;25(3):454-61. doi: 10.1097/EDE.0000000000000075. PMID: 24608666; PMCID: PMC3984024.
	The discussion raises important ad interesting points about a possible role for fat distribution and inflammation. It however ignores other important explanations (e.g. Athavale P, Kumar V, Clark J, Mondal S, Sur S. Differential Impact of COVID-19 Risk Factors on Ethnicities in the United States. Front Public Health. 2021 Dec 6;9:743003. doi: 10.3389/fpubh.2021.743003. PMID: 34938701; PMCID: PMC8687082.). The limitations in the bullet points could be expanded in the discussion to include issues such as the impact of obesity and ethnicity on non-hospitalised patients – whether undiagnosed (and thus probably less severe), uninsured, or less able to access medical care for other reasons.
	Minor points:
	Page 6, L14-15 and subsequent. The terms reduced and increased imply a change or intervention and would better be replaced with lower and higher.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Kengo Nagashima, Keio University Hospital
Comments to the Author:
In this manuscript, the authors investigated ethnic minorities, obesity (BMI) and their interaction with hospitalization, invasive ventilation and mortality for COVID-19. Statistical analyses were generally conducted appropriately, but I have a few comments.

1. Categorization of continuous variables
Since categorization of continuous variables is known to be problematic, it is better to also perform the analysis using continuous variables.

Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ 2006; 332: 1080. DOI: https://doi.org/10.1136/bmj.332.7549.1080

We thank you for bringing this to our attention. Our variables include age, geocoding income and BMI which are continuous variables but we categorized them. While we agree that categorization of continuous variables may be problematic, BMI is oftentimes categorized. Using categorical variables results in less statistical power due to information lost or reduced precision. Fortunately, we do have a very large sample and the effect of age, geocoding, income and BMI in our outcomes can still be clearly demonstrated.

2. Missing data
Since the method for handling missing data is not described, please add a description of how to address missing data.
If you were conducted complete-case analyses, it would be desirable to consider applying multiple imputation or other appropriate methods as sensitivity analyses.
A description of how we addressed missing data was included in the methods and results sections.

3. STROBE Statement checklist
Please add item 12 as it is blank.
Item 12 was completed on the STROBE Statement check list

Reviewer: 2
Dr. Indrikis Krams, University of Tartu
Comments to the Author:
bmjopen-2021-059132

This is a precious and well-written paper. It will be of interest to the wide community of physicians and biomedical scientists. I have only one comment, and I believe the paper can be published almost as it stands.

My lab has recently proposed an idea of a more severe outcome of the COVID-19 disease in Western countries which is based on differences in the fattening strategies between Asians and Europeans. The amount of visceral adipose tissue (VAT) is among the most important predictors in our theoretical research. You wrote that "When we adjusted BMI for Asian patients, we did not find a striking difference in trends in our results…". Could you please elaborate more on your results in light of our hypothesis?

We thank you for your comments. Elaboration of these results from adjusted BMI for Asian patients was provided in the discussion section as below

When we adjusted BMI for Asian patients, we did not find a striking difference in trends compared to results with standard cut off points except for a few instances when examining the risk of invasive ventilation and death. While Asian patients with a BMI of 44-44.9 kg/m² had a 4.5 times higher risk of invasive ventilation compared to Asian patients with a normal BMI, this risk was 6.6 times higher in Asian patients with a BMI between 37.5-42.4 kg/m² compared to Asian patients with a BMI under 23 kg/m² (eTable 2). The risk of mortality was 4.0 times greater for Asian patients with a BMI above 45 kg/m² and 3.0 times greater when the BMI was adjusted to above 42.5 kg/m² (eTable 2).

As far as I understood, you did not measure VAT directly in your study?

Clarification was provided indicating SAT and VAT were not directly measured in this study

Please, consider the following papers of my lab:
Krams et al. 2021 Int J Environ Res Public Health 18: 1029. doi.org/10.3390/ijerph18031029
Krams et al. 2020 Pathogens 9: 887. doi.org/10.3390/pathogens9110887

Krams et al. 2018. J Exp Biol 221. doi: 10.1242/jeb.184499
Papers from your lab provided valuable information. One study was referenced in the manuscript.

Reviewer: 3
Prof. Nicholas Finer, UCL
Comments to the Author:
The authors have examined the KP Southern California health records to explore the impact of obesity and ethnicity on COVID-19 severity. These are important findings that have both clinical and research implications.

Major points:

There is no information on vaccination status which surely differs between age and ethnic groups?
While the vaccine was approved in certain populations by the FDA in December 2020, it was not widely available in the United States until March of 2021. As such, our study took place prior to the vaccine being readily accessible.

https://ourworldindata.org/covid-vaccinations

The paper is not written in patient-first language e.g. obese Black patients should be Black patients with obesity. (e.g., https://odr.dc.gov/page/people-first-language);

We have now applied patient first language throughout the manuscript.

morbid obesity is an archaic term – severe obesity is preferred.
We agree this is an archaic term so this term was removed from the manuscript.

Most of the positive findings relate to those with a BMI >40 or >45. As such should the title be '…with SEVERE obesity…'?
We agree and so severe obesity is now included in the title.

With the now (2022) dominance of the (probably milder) omicron variant, it might be worth including a mention of the dominant strain of COVID-19 present at the time of the study.
Information was provided indicating the epsilon strain was dominant during a winter surge between November 2020 and March 2021

There is much focus (in the discussion) of a potential 'obesity paradox'. Firstly, many prefer the term 'BMI paradox' to obesity paradox, since it is the wide variance of %body fat at any BMI that may contribute to the 'paradox'.

We agree with you and so the term obesity paradox has been changed to BMI paradox.

Although the authors allude to, and cite some of the literature on the contrary findings relating BMI to severity and outcomes, they do not address the fundamental flaws (such as reverse causality, collider bias etc.) around this concept, that in this reviewer's opinion hugely undermine its validity, e.g. some of many publications

Peeters A. Journals should no longer accept 'obesity paradox' articles. Int J Obes (Lond). 2018;42:584-5. doi: 10.1038/ijo.2017.259

Martin-Ponce E, Santolaria F, Aleman-Valls MR, Gonzalez-Reimers E, Martinez-Riera A, Rodriguez-Gaspar M, et al. Factors involved in the paradox of reverse epidemiology. Clin Nutr. 2010;29:501-6. doi: 10.1016/j.clnu.2009.12.009

Vansteelandt S. Asking Too Much of Epidemiologic Studies: The Problem of Collider Bias and the Obesity Paradox. Epidemiology. 2017 Sep;28(5):e47-e49. doi: 10.1097/EDE.0000000000000693. PMID: 28574920.

De Jong A, Wrigge H, Hedenstierna G, Gattinoni L, Chiumello D, Frat JP, Ball L, Schetz M, Pickkers P, Jaber S. How to ventilate obese patients in the ICU. Intensive Care Med. 2020 Dec;46(12):2423-2435. doi: 10.1007/s00134-020-06286-x. Epub 2020 Oct 23. PMID: 33095284; PMCID:

Lee DH, Giovannucci EL. The Obesity Paradox in Cancer: Epidemiologic Insights and Perspectives. Curr Nutr Rep. 2019 Sep;8(3):175-181. doi: 10.1007/s13668-019-00280-6. PMID: 31129887.

Preston SH, Stokes A. Obesity paradox: conditioning on disease enhances biases in estimating the mortality risks of obesity. Epidemiology. 2014 May;25(3):454-61. doi: 10.1097/EDE.0000000000000075. PMID: 24608666; PMCID: PMC3984024.

We indeed agree that flaws exist with the concept of BMI paradox. To address this we have included the following additional information below in our manuscript.

In our study, a BMI paradox was not observed in any ethnicity with a BMI greater than or equal to 45 kg/m². Risk of death at the highest BMI category in our study was disproportionately elevated in minority ethnic groups - 2.8 times greater in Black patients, 3.0 times greater in Hispanic patients, 4.0 times greater in Asian patients and 4.6 times greater in Pacific Islander patients compared to a 1.5 times greater risk in White patients who had a BMI greater than or equal to 45 kg/m² (Figure 3). Further, reports have identified fundamental flaws including collider bias and reverse causality that compromise the validity of a BMI paradox,[28-31].

The discussion raises important and interesting points about a possible role for fat distribution and inflammation. It however ignores other important explanations (e.g. Athavale P, Kumar V, Clark J, Mondal S, Sur S. Differential Impact of COVID-19 Risk Factors on Ethnicities in the United States. Front Public Health. 2021 Dec 6;9:743003. doi: 10.3389/fpubh.2021.743003. PMID: 34938701; PMCID: PMC8687082.).

We thank you for this comment. We agree that other important explanations should be included. The following was added to the manuscript to address additional valuable explanations for poor outcomes due to COVID-19:

Other important explanations for poor outcomes associated with COVID-19 among different ethnicities have been identified. Previous reports indicate diabetes and advanced age were associated with increased risk factors of infection with COVID-19 particularly in Hispanic patients,[41]. We observed an increased risk of unfavorable outcomes in patients with diabetes, but this risk was overshadowed in patients with severe obesity (eFigures 2-4). Our report found a significantly increased risk of severe disease and death in patients over the age of 81 compared to patients between the ages of 51-60 (eFigure 4). Poverty, which has been identified as an independent risk factor for COVID-19, has been shown to result in an increased risk of infection among White, Black and Hispanic patients,[41]. Our results indicate wealthier patients who earned over $100,000 experienced a lower risk of hospitalization and death due to COVID-19 (eFigures 2,4).

Additional reports suggest Asian and Hispanic patients may experience barriers to quality and timely care due to various factors including limitations in English proficiency,[7,10]. The COVID-19 pandemic led to a surge in patients seeking care by telemedicine. Disparities in telehealth use have been identified indicating utilization was lower in Hispanic and Asian patients and higher in black

patients,[42-44]. Reports have also found telehealth use was higher in black patients with obesity during the pandemic,[45].

The limitations in the bullet points could be expanded in the discussion to include issues such as the impact of obesity and ethnicity on non-hospitalised patients – whether undiagnosed (and thus probably less severe), uninsured, or less able to access medical care for other reasons.

We agree this is an important point to address. Clarity was provided regarding inclusion of non hospitalized patients in our study in both the strengths and limitations portion of the manuscript. We also expanded on these strengths and limitations in the discussion.
Strengths

- This study included a large, diverse cohort from Kaiser Permanente Southern California - an integrated health care system where access to care may have been more uniform.
- We were able to accurately obtain information from virtual, outpatient and inpatient care streams in our patients through a robust electronic medical record system.

Limitations

- Our cohort was made up of COVID-19 positive patients defined as having a diagnosis of COVID-19 or having a positive test processed in our laboratory. Some patients who tested positive outside of Kaiser Permanente Southern California or not tested at all may have been missed.
- Patients with COVID-19 who lack insurance, did not pursue testing, or encountered barriers to testing and medical evaluation were not accounted for in this study.
- Some patients who did not have a BMI on record or were categorized as having "other" ethnicity were not accounted for. Further, the representation of Pacific Islander patients in our cohort was small.

This study has many important strengths. We included a large cohort from an integrated health care system where access to care is expected to be more uniform. With the use of a robust electronic medical record system, we accurately obtained information from virtual, outpatient and inpatient platforms. This report also has limitations. Patients who tested positive outside of KPSC, were undiagnosed or encountered barriers to care were not included. Further, we did not include patients who lacked a BMI on file or had an ethnicity listed as other. We also noted the representation of Pacific Islander patients was small compared to other ethnicities in our cohort.

Minor points:

Page 6, L14-15 and subsequent.
The terms reduced and increased imply a change or intervention and would better be replaced with lower and higher.
the terms higher and lower replaced increased and reduced respectively

VERSION 2 – REVIEW

REVIEWER	Kengo Nagashima Keio University Hospital, Biostatistics Unit, Clinical and Translational Research Center
REVIEW RETURNED	30-Apr-2022

GENERAL COMMENTS	I have no additional comments.

REVIEWER	Nicholas Finer UCL, Bariatric Medicine and Surgery

REVIEW RETURNED	27-Apr-2022

GENERAL COMMENTS	Thank you for addressing the issues raised by myself and the other reviewers.